Remarks

Applicants appreciate the withdrawal of the rejection of claims 56 and 57 under 35 U.S.C. § 112, second paragraph and the rejection of claims 28-32 and 51-60 under 35 U.S.C. § 112, first paragraph.

Claim Construction and Amendments

The Office Action has construed the claims as reciting a molecular complex that "comprises at least four fusion proteins that are ***either*** an Ig variable heavy chain and an extracellular portion of a transmembrane polypeptide ***or*** an Ig variable light chain and an extracellular portion of a transmembrane polypeptide." *See* Paper No. 16, paragraph bridging pages 5 and 6, and page 6, second full paragraph (emphasis added). The Office Action also has construed the claims as reciting a molecular complex that "comprises "at least four fusion proteins, wherein the fusion proteins comprise ***either*** an Ig heavy chains [sic] and a transmembrane polypeptide ***or*** an Ig light chain and a transmembrane polypeptide." *See* Paper No. 16, page 3, last paragraph (emphasis added). Neither construction is correct.

The recited molecular complex comprises at least two of each of the two recited types of fusion protein. To clarify this point, claim 28 is amended to recite that the molecular complex comprises "at least two first and at least two second fusion proteins." Claim 28 also is amended to clarify that "each ligand binding site is formed by the extracellular domain of a first transmembrane polypeptide and the extracellular domain of a second transmembrane polypeptide." These amendments are supported by the language of the original claim. The amendments do not add new matter and do not narrow the scope of claim 28.

The Rejection of Claims 28-32 and 51-60 Under 35 U.S.C. § 112, second paragraph

Claims 28-32 and 51-60 stand rejected under 35 U.S.C. § 112, second paragraph. Applicants respectfully traverse the rejection.

The Office Action asserts that "it is unclear as to how the extracellular domain of the transmembrane polypeptide forms the binding domains when the said [sic] polypeptide is linked or conjugated to the variable domains of an immunoglobulin. Does steric hinderance from the variable domains of an immunoglobulin interfere with the binding of ligands to the extracellular domain of the transmembrane protein?" Paper No. 16, paragraph bridging pages 2 and 3.

First, Applicants wish to clarify that each ligand binding site is formed by two extracellular domains of transmembrane polypeptides. See claim 28: "each ligand binding site is formed by the extracellular domain of a first transmembrane polypeptide and the extracellular domain of a second transmembrane polypeptide." Applicants also wish to clarify that claim 28 does not require that either the first or the second transmembrane polypeptide be "linked or conjugated to the variable domains of an immunoglobulin." The first fusion protein comprises an immunoglobulin heavy chain and an extracellular portion of a first transmembrane polypeptide. The immunoglobulin heavy chain comprises a variable region, but claim 28 does not specify that the transmembrane polypeptide is linked or conjugated to its variable domain. *See also* dependent claims 53 and 54, which recite a peptide linker between the immunoglobulin heavy chain and the extracellular domain of the first transmembrane polypeptide. The second fusion protein comprises an immunoglobulin light chain and an extracellular portion of a second transmembrane polypeptide; a variable region of an immunoglobulin light chain is not a required element of the second fusion proteins. *See, e.g.*, Figures 1A-1D.

Second, the Office Action's speculation about steric hindrance does not render claims 28-32 and 51-60 unclear. In fact, the specification teaches that steric hindrance is not a problem:

> Successful expression of soluble molecular complexes with high avidity for their cognate ligands is achieved using an immunoglobulin as a molecular scaffolding structure. The immunoglobulin moiety serves as a scaffolding for proper folding of the α and β chains, without which nonfunctional aggregates would likely result, as previously described (4, 12). The physical proximity of the immunoglobulin heavy and light chains, whose folding and association is favored by a net gain in free energy, overcomes the entropy required to bring the soluble TCR or MHC a and b chains together to facilitate their folding. Furthermore, the intrinsic flexibility afforded by the immunoglobulin hinge region facilitates the binding of the ligand binding sites to their cognate ligands.

Page 14, lines 8-18.

Claims 28-32 and 51-60 are clear and definite. Applicants respectfully request withdrawal of the rejection.

The Rejections Under 35 U.S.C. § 102(b)

The Office Action makes the following rejections under 35 U.S.C. § 102(b):

- claims 28, 30-32, 53, and 56 stand rejected under 35 U.S.C. § 102(b) over Kuwana *et al.*, *Biochem. Biophys. Res. Commun. 149*, 960-68, 1987 ("Kuwana");
- claims 28, 30, and 31 stand rejected under 35 U.S.C. § 102(b) over Seimiya *et al.*, *J. Biochem. 113*, 687-91, 1993 ("Seimiya"); and
- claims 28, 29, 31, 32, 51, and 56 stand rejected under 35 U.S.C. § 102(b) over Zwirner *et al.*, *J. Immunol. 148*, 272-76, 1992 ("Zwirner").

Applicants respectfully traverse each of these rejections.

To anticipate a claim under 35 U.S.C. § 102, each and every element as set forth in the claim must be either expressly or inherently described in a single prior art reference. *Verdegaal*

Bros. v. Union Oil Co. of California, 814 F.2d 628, 631 (Fed. Cir. 1987). Neither Kuwana, Seimiya, or Zwirner discloses each element of independent claim 28.

Independent claim 28 is directed to a composition comprising a cell having a molecular complex bound to its surface. The molecular complex comprises at least two first fusion proteins and at least two second fusion proteins. The first fusion protein comprises an immunoglobulin heavy chain and an extracellular portion of a first transmembrane polypeptide; the immunoglobulin heavy chain comprises a variable region. The second fusion protein comprises an immunoglobulin light chain and an extracellular portion of a second transmembrane polypeptide. The at least two first fusion proteins and the at least two second fusion proteins associate to form a molecular complex that comprises two ligand binding sites. Each ligand binding site is formed by the extracellular domain of a first transmembrane polypeptide and the extracellular domain of a second transmembrane polypeptide.

The rejection of claims 28, 30-32, 53, and 56 over Kuwana

Kuwana is cited as teaching "an EL4 cell that expresses a chimeric receptor on the surface of the said [sic] cell, comprising variable light chain linked to TCR β, variable heavy chain linked to TCR β, variable light chain linked to TCR α, and variable heavy chain linked to TCR β." Paper No. 16, page 5, first full paragraph. Kuwana also is cited as teaching "the linking of the fusion protein by a linker" and "mixing/incubating EL4 cells with an antigenic peptide." *Id.*

The proteins encoded by Kuwana's chimeric genes are not the same as the fusion proteins of the molecular complex recited in independent claim 28. Kuwana expressed "[c]himeric genes composed of immunoglobulin (Ig)-derived variable (V) regions and T-cell receptor (TCR)-

derived constant (C) regions." Abstract. The portion of Kuwana's chimeric proteins capable of binding an antigen thus is formed by immunoglobulin variable regions because no variable regions of the TCR are included. *See* Novotny *et al.*, *Proc. Natl. Acad. Sci. USA 88*, 8646-50, 1991 (attached), which explains that antigen binding sites of both immunoglobulins and TCR are formed by the variable regions of these proteins. In contrast, each of the ligand binding sites recited in independent claim 28 is formed by the extracellular domain of a first transmembrane polypeptide and the extracellular domain of a second transmembrane polypeptide (*e.g.*, a TCR α and β chain, as recited in dependent claim 30).

Second, Kuwana's chimeric molecule contains only two fusion proteins. In contrast, the molecular complex recited in independent claim 28 contains at least two of each of two first fusion proteins and at least two second fusion proteins, *i.e.*, at least four fusion proteins. Each of Kuwana's chimeric molecules contains only one binding site, whereas the recited molecular complex contains two ligand binding sites.

Kuwana also does not disclose a pharmaceutically acceptable carrier, as recited in dependent claim 31.

Kuwana does not disclose each recited element of independent claim 28. Thus, Kuwana does not anticipate the subject matter of independent claim 28 or of dependent claims 30-32, 53, and 56. Applicants respectfully request withdrawal of the rejection over Kuwana.

The rejection of claims 28, 30, and 31 over Seimiya

Seimiya is cited as disclosing "SP2/0 myeloma cells expressing a TCR-α or β protein linked to Ig molecule." Paper No. 16, first full paragraph. Seimiya does not disclose any of the fusion proteins of the recited molecular complex. Seimiya "created genetic constructs encoding

a chimeric antibody Fab fragment in which mouse immunoglobulin constant regions from a phosphorylcholine-specific antibody were substituted for human αβ-T cell receptor (TCR) extracellular constant regions (for solubilization, the transmembrane- and cytoplasmic-regions of the receptor were deleted). These constructs, *i.e.*, chimeric heavy ($V_HC_\beta C_\kappa$) and light (V_LC_α) chains, were cotransfected into murine SP2/0 myeloma cells for expression." Abstract. *See also* the schematic in Figure 1, page 688. The portion of Seimiya's chimeric Fab fragment capable of binding an antigen thus is formed by immunoglobulin variable regions because no variable regions of the TCR are included. *See* Novotny *et al.*, 1991 (attached). In contrast, each of the ligand binding sites recited in claims 28, 30, and 31 is formed by the extracellular domain of a first transmembrane polypeptide and the extracellular domain of a second transmembrane polypeptide (*e.g.*, a TCR α and β chain, as recited in dependent claim 30).

Furthermore, Seimiya's chimeric molecule contains only two fusion proteins. In contrast, the recited molecular complex contains at least two of each of two first fusion proteins and at least two second fusion proteins, *i.e.*, at least four fusion proteins. Each of Seimiya's chimeric molecules contains only one binding site, whereas the recited molecular complex contains two ligand binding sites.

Seimiya also does not disclose a pharmaceutically acceptable carrier, as recited in dependent claim 31.

Seimiya does not teach the molecular complex recited in independent claim 28. Thus, Seimiya does not anticipate the subject matter of independent claim 28 or of dependent claims 30 and 31. Applicants respectfully request withdrawal of the rejection over Seimiya.

The rejection of claims 28, 29, 31, 32, 51, 56, and 60 over Zwirner

Zwirner is cited as teaching "a mouse B-cell lymphoma cell line (A20) expressing a chimeric MHC class II-Ig fusion protein wherein the MHC class II are α or β chains and the Ig is of the IgG1 subtype." Paper No. 16, paragraph bridging pages 6 and 7. Zwirner teaches two fusion proteins. One fusion protein contains a variable domain of an immunoglobulin light chain and a portion of an MHC class II α chain. Abstract. The other fusion protein contains a variable domain of an immunoglobulin heavy chain and a portion of an MHC class II β chain. *Id.* The two types of fusion protein can be expressed on a cell surface and associate to form a "chimeric molecule" that binds an anti-idiotypic antibody. *Id.* The portion of Zwirner's chimeric molecules capable of binding an anti-idiotypic antibody thus is formed by immunoglobulin variable regions because no variable regions of the TCR are included. *See* Novotny *et al.*, 1991 (attached). In contrast, each of the ligand binding sites recited in independent claim 28 is formed by the extracellular domain of a first transmembrane polypeptide and the extracellular domain of a second transmembrane polypeptide (*e.g.*, an MHC class IIβ chain and an MHC class IIα chain, as recited in dependent claim 29).

Furthermore, Zwirner's chimeric molecule contains only two fusion proteins. In contrast, the recited molecular complex contains at least two of each of two first fusion proteins and at least two second fusion proteins, *i.e.*, at least four fusion proteins. Each of Zwirner's chimeric molecules contains only one binding site, whereas the recited molecular complex contains two ligand binding sites.

Zwirner also does not disclose a pharmaceutically acceptable carrier, as recited in dependent claim 31.

Zwirner does not disclose each recited element of independent claim 28. Thus, Zwirner does not anticipate the subject matter of independent claim 28 or of dependent claims 29, 31, 32, 51, 56, and 60. Applicants respectfully request withdrawal of the rejection over Zwirner.

The Rejection of Claims 28-32, 51-53, 56, 58, and 60 Under 35 U.S.C. § 103(a)

Claims 28-32, 51-53, 56, 58, and 60 stand rejected under 35 U.S.C. § 103(a) over the combination of Kuwana, Zwirner, and Selick (WO 93/10220; "Selick"). Applicants respectfully traverse the rejection.

The U.S. Patent and Trademark Office bears the initial burden of establishing a *prima facie* case of obviousness. The *prima facie* case requires three showings:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Manual of Patent Examining Procedure, 8th ed., § 2142. In the present application, a *prima facie* case that claims 28-32, 51-53, 56, 58, and 60 are obvious has not been made because the ordinary artisan would have had no motivation to have combined the teachings of Kuwana, Zwirner, and Selick.

The Office Action asserts that "[o]ne would have been motivated to combine the references because the references teach the utilization of a composition that comprises α and β subunits of MHC or TCR molecules fused with antibody fragments." Page 8, lines 7-9. The asserted motivation is legally insufficient.

Neither Kuwana nor Zwirner teaches or suggests a molecular complex comprising at least two of each of the two types of fusion protein recited in independent claim 28 (*i.e.*, at least four fusion proteins). None of the chimeric molecules disclosed in either Kuwana or Zwirner contains more than two fusion proteins. Neither Kuwana nor Zwirner suggests that the disclosed chimeric molecules should be modified to include four fusion proteins. Moreover, neither Kuwana nor Zwirner teaches or suggests a chimeric molecule containing two ligand binding sites formed by the extracellular domains of two transmembrane polypeptides. All the chimeric molecules taught in Kuwana and Zwirner have binding sites formed by immunoglobulin variable domains. In contrast, Applicants' molecular complex contains ligand binding sites formed by the extracellular domain of a first transmembrane polypeptide and the extracellular domain of a second transmembrane polypeptide (*e.g.*, an MHC class IIβ chain and an MHC class IIα chain, as recited in dependent claim 29, or a TCR α and β chain, as recited in dependent claim 30). If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 813, 123 U.S.P.Q. (BNA) 349, 352, (C.C.P.A. 1959).

Selick does not remedy the deficiencies of Kuwana and Zwirner. Selick does disclose a molecule comprising four fusion proteins in which two binding sites are formed by extracellular domains of MHC class II α and β chains. Selick, however, does not provide sufficient motivation to combine its teachings with those of either Kuwana or Zwirner. First, Selick teaches "chimeric proteins comprising an MHC component linked to an immunoglobulin constant region component." Abstract. The chimeric proteins do not contain the variable region

of an immunoglobulin heavy chain, as recited in independent claim 28. Selick provides no motivation to include the variable region. In fact, Selick explicitly teaches that less than 10 amino acids of the variable region should be included: "As defined here, the constant region component may also comprise a portion of the variable region of the particular immunoglobulin chain, usually less than about 10 amino acids." Page 9, lines 26-29. Thus, the teachings of Selick cannot be combined with those of Kuwana or Zwirner, both of which teach chimeric proteins that include variable domains of immunoglobulins.

Second, Selick provides no motivation to make a composition comprising a cell in which a molecular complex is bound to the surface of the cell. On the contrary, Selick teaches that the invention provides "soluble chimeric proteins." Page 3, lines 6-7. *See also* the sentence bridging pages 2 and 3: "The prior art lacks a soluble agent capable of blocking MHC restricted T cell activation, which agent inter alia has an extended serum half-life and provides a mechanism for eliminating targeted T cells without the necessity of using toxic conjugates."

The Office Action has merely selected elements from the cited references and combined them using applicants' disclosure as a template. Such hindsight use of the specification is not permitted. *Texas Instruments Inc. v. U.S. ITC* 988 F.2d 1165, 1178 (Fed. Cir. 1993).

The U.S. Patent and Trademark Office has not established a *prima facie* case that claims 28-32, 51-53, 56, 58, and 60 are obvious over the combination of Kuwana, Zwirner, and Selick. Applicants respectfully request withdrawal of the rejection.

The Obviousness-Type Double-Patenting Rejection of Claims 28-32 and 51-60

Claims 28-32 and 51-60 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-10 of U.S. Patent 6,015,884 ("the '884 patent") in view of Seimiya. Applicants respectfully traverse the rejection.

The present application was filed with 50 claims. Claims 1-16, now canceled, were directed to the molecular complex. In a restriction requirement mailed December 11, 2001, claims 1-16 were placed into a separate invention group (Group I) from the claims now pending. Thus, the U.S. Patent and Trademark Office already has determined that the subject matter being prosecuted in this application is patentable over claims to the molecular complex itself.

The subject matter of claims 1-10 of the '884 patent corresponds to claims 1-9 and 14 of the canceled Group I claims. Thus, an obviousness-type double patenting rejection over claims 1-10 of the '884 patent in view of Seimiya is improper.

Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,

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